AMENDMENTS AND UPDATES TO HUMAN GENE TRANSFER PROTOCOLS

RECOMBINANT DNA ADVISORY COMMITTEE MEETING
September 2001

ID #	Letter	Protocol #	Amendment Description
		9303-040	**Phase I Study of Non-Replicating Autologous Tumor Cell Injections Using Cells Prepared With or Without Granulocyte-Macrophage Colony Stimulating Factor Gene Transduction in Patients with Metastatic Renal Cell Carcinoma.**
225	07/16/2001		*Annual Update:* Received annual reports for the following protocols: 9303-040, 9408-082, and 9411-093.
		9411-092	**High Dose Chemotherapy and Autologous Bone Marrow plus Peripheral Blood Stem Cell Transplantation for Patients with Lymphoma or Metastatic Breast Cancer: Use of Marker Genes to Investigate the Biology of Hematopoietic Reconstitution in Adults.**
210	06/13/2001		*Status Change:* Notification from PI that trial is closed.
		9503-103	**Gene Therapy for AIDS using Retroviral Mediated Gene Transfer to Deliver HIV-1 Antisense TAR and Transdominant Rev Protein Genes to Syngeneic Lymphocytes in HIV Infected Identical Twins.**
201	07/03/2001		*PI or Site Change:* Dr. Morgan is no longer a PI for this trial. Dr. Tavel is now the sole PI.
		9506-109	**Treatment of Patients with Advanced Epithelial Ovarian Cancer using Anti-CD3 Stimulated Peripheral Blood Lymphocytes Transduced with a Gene Encoding a Chimeric T-cell Receptor Reactive with Folate Binding**
208	08/01/2001		*Protocol Change:* Amendment for intra-arterial administration of study agent to a single individual. A copy of the revised clinical protocol and informed consent were sent to Drs. Greenblatt, Markert, and Mickelson for review. RAC members comments were going to be conveyed to the to the investigator.

ID #	Letter	Protocol #	Amendment Description	
		9510-129	**Administration of Neomycin Resistance Gene Marked EBV Specific Cytotoxic T Lymphocytes as Therapy for Patients Receiving a Bone Marrow Transplant for Relapsed EBV-Positive Hodgkin Disease.**	
173	08/08/2001		*Protocol Change:*	Clinical protocol has been amended to clarify long-term follow-up to meet the current recommendations of the FDA. In addition, the eligibility criteria have been amended to state that: "Any patient with EBV positive Hodgkin disease, in second relapse regardless of age or sex, in first relapse or with primary disease, or in first remission if immunosuppressive chemotherapy is contraindicated, e.g. patients who develop Hodgkin disease after solid organ transplantation or if Hodgkin's is a second malignancy e.g. aa Richters transformation of CLL."
229	08/08/2001		*Protocol Change:*	Long-term follow-up has been clarified. For individuals who participate in the gene marking portion of the trial, follow-up will be for life. For individuals who are not participating in the gene marking portion, follow-up will be for one year.
		9706-196	**Fibronectin-Assisted, Retroviral-Mediated Transduction of CD34+ Peripheral Blood Cells with gp91 phox in Patients with X-Linked Chronic Granulomatous Disease: A Phase I Study.**	
155	05/30/2001		*Annual Update:*	Received a copy of IRB-approved continuing review. To date, two individuals have been enrolled in this trial. One individual is 17 months and the other is 24 months post-infusion. Both are clinically well, as reported by the PI, compared to their baselines.
192	07/06/2001		*Annual Update:*	Received a copy of the FDA annual report.
		9708-205	**Phase I/II Study of Allogeneic Human GM-CSF Gene Transduced Irradiated Prostate Cancer Cell Vaccines in Patients with Prostate Cancer.**	
186	07/23/2001		*Status Change:*	Letter from sponsor that this trial is closed. Individuals enrolled in this study have been requested to enroll in long-term follow-up. An annual report was submitted to OBA in June 2000. The sponsor has indicated that since the June 2000 annual report, there has been no further activity on this trial. Therefore, there are no plans to submit further reports relating to this trial.

ID #	Letter	Protocol #	Amendment Description
		9709-210	**Compassionate Use Protocol for Retreatment with Allovectin-7 Immunotherapy for Metastatic Cancer by Direct Gene Transfer. Sponsor: Vical, Inc.**
149	06/08/2001		*PI or Site Change:* Dr. Edward Levine at Wake Forest University School of Medicine is now an investigator on this
		9709-213	**A Phase II Study of Autologous CD4-Zeta Gene-Modified T Cells in HIV-Infected Patients with Undectable Plasma Viremia on Combination Antiretroviral Drug Therapy. Sponsor: Cell Genesys, Inc.**
226	07/13/2001		*Status Change:* Trial is now closed to new accrual, follow-up is continuing for enrolled individuals.
			Annual Update: A summary of the experiences gained from this study will be presented at the September meeting by Dr. Ando.

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		9801-230	**Evaluation of the Safety and Effects of Ex Vivo Modification and Re-infusion of CD34+ Cells by an Antisense Construct Against HIV-1 in a Retroviral Vector. Sponsor: Enzo Therapeutics, Inc.**
207	05/18/2001		*Annual Update:* The study planned to enroll 8 HIV+ patients, with the initial 3 patients receiving a single re-infusion of their ex-vivo modified CD34+ cells (modified by an antisense construct against HIV-1 delivered via a retrovirus vector) and the remaining 5 patients to receive multiple re-infusions if there were no significant adverse events seen in the initial cohort. The total number of patients enrolled to date is deleted in this annual report (this information considered confidential) but enrollment has occurred in the multiple re-infusion phase of this study. In regard to adverse events, one patient was diagnosed with rectal cancer approximately 3 months after receiving his one re-infusion. This patient was previously reported to us and the cancer was considered to be unrelated to the gene transfer product. Since the last annual report, the patient has been lost to follow-up and has been terminated from the study. One subject experienced the following adverse events: moderate rash (resolved on its own), moderate leukoplakia (resolved on its own) and severe tremors (secondary to stopping Depakote). Another subject experienced all of the following mild adverse events: stomach ache (resolved on its own), watery diarrhea (resolved on its own and attributed to a viral gastroenteritis) and mild plantar warts (treated with trichloroacetic acid). As per the principal investigators none of the adverse events could be related to receipt of the vector. In regard to efficacy, the antisense construct was shown to be present and functioning in subjects' peripheral bone marrow cells. However, no significant change in the number of CD4+ cells or in the HIV viral load has been noted. I reviewed our files and in addition to the adverse events noted above, there was a report from March 16, 2000 in which a patient attempted suicide due to "personal relationship problems." No further follow-up on this patient is noted.

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		9802-233	**Phase II Study of Direct Gene Transfer of HLA-B7 Plasmid DNA/DMRIE/DOPE Lipid Complex (Allovectin-7) as an Immunotherapeutic Agent in Patients with Stage III or IV Melanoma with No Treatment Alternatives. Sponsor: Vical, Inc.**	
209	05/24/2001		*PI or Site Change:*	Notification that Dr. Sabina Wallach has replaced Dr. Bernstein as the PI at the Scripps Memorial Hospital site in San Diego, La Jolla, and Encinitas, CA.
		9802-237	**Molecular Synovectomy by In Vivo Gene Transfer: A Phase I Trial.**	
171	06/13/2001		*Annual Update:*	Received a copy of the annual report as submitted to the FDA.
		9805-251	**Phase I/II Trial of Antigen-Specific Immunotherapy in MUC-1 Positive Patients with Adenocarcinoma of the Prostate Using Vaccinia Virus-MUC1-IL2 (TG 1031). Sponsor: Transgene, S.A.**	
166	06/18/2001		*Protocol Change:*	Individuals on study after 12 months post study agent administration without grade 3 or 4 toxicities will be assessed by a physician every 3 months. Safety assessments (performed by a nurse) and laboratory tests will continue to be performed on a monthly basis. In addition, protocol was amended to permit a single individual to have study agent readministered. This individual was not taken off study. This individual's PSA levels dropped initially, remained stable for 9 months, but had doubled 6 months following last administration of study agent. This individual will be tested for anti-vaccinia virus antibodies, prior to readministration of the study agent.
		9805-253	**A Phase II Study of Autologous CD4-Zeta Gene-Modified T Cells in HIV Infected Patients with Undetectable Plasma Viremia on Highly Active Anti-Retroviral Drug Therapy Sponsor: Cell Genesys, Inc.**	
227	07/13/2001		*Status Change:*	Trial is now closed to new accrual, follow-up is continuing for enrolled individuals. A summary of the experiences gained from this study will be presented at the September meeting by Dr. Ando.

ID #	Letter	Protocol #	Amendment Description	
		9901-280	**A Phase II/III Trial of Chemotherapy Alone Versus Chemotherapy Plus SCH 58500 in Newly Diagnosed Stage III Ovarian and Primary Peritoneal Cancer Patients with >0.5 cm and <2 cm Residual Disease Following Surgery. Sponsor: Schering Corporation**	
158	05/21/2001		*PI or Site Change:*	Dr. Joseph Lucci has replaced Dr. Joseph Santosa as the PI at the University of Texas Medical Branch, Galveston, TX.
148	05/30/2001		*Status Change:*	Letter from IRB chair at the University Medical Center of Southern Nevada indicating that due to an unfavorable risk to benefit ratio (based upon an analysis of 114 individuals enrolled in this multi-site trial), that individuals at this site would be removed from the study and given
188	07/24/2001		*Status Change:*	Notification that at two registered sites, trial is closed to new enrollment. Follow-up is continuing. Closed sites are: University of Pittsburgh, PI is Dr. Edwards and Greenville Hospital System, PI is Dr. Puls.
228	08/09/2001		*Status Change:*	Notification that this trial has been closed at the University of Kentucky site; PI: Dr. Holly Gallion

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		9902-285		**A Phase I Trial of Intratumoral Antisense EGFR DNA and DC-Chol Liposomes in Advanced Oral Squamous Cell Carcinoma.**
157	06/14/2001		*Annual Update:*	Received copy of the latest version of the clinical protocol that has been approved by the IRB.
178	07/27/2001		*Annual Update:*	Received a copy of the latest clinical protocol. And an update of the status of this trial--see UAI 176
177	08/03/2001		*Other:*	Received a copy of the minutes of the University of Pittsburgh Data Safety Monitoring Committee meeting held to review the problem with the vector used (see UAI 176).
176	08/08/2001		*Status Change:*	The following information was provided by the University of Pittsburgh: "This phase I study was suspended by the investigator July 23, immediately after the investigator learned that the participants in the trial were given a control plasmid in combination with DC-Chol liposomes. The control plasmid contained the EGFR antisense sequence in the reverse orientation (i.e. the sense orientation). Preclinical studies in the laboratory using this vector have found no effects on modulation of gene expression or tumor growth. The clinical site has commenced two internal audits: one to review the research and medical records of the study to validate the investigator's conclusions that no toxicities were observed related to the gene transfer intervention and that all deaths were related to progression of the underlying disease; and one to review the procedures in the laboratory where the plasmid was produced. The clinical site will issue its report and recommendations as soon as the audits are complete. "Thirteen oral cancer patients, non-responsive to currently available treatments, were accrued to the study and ten patients completed participation in the research study. There were no protocol-associated toxicities observed and no clinical responses were detected. There are no subjects currently receiving the gene transfer product. Eleven of the patients subsequently *Annual Update:* died of disease progression. All deaths occurred after the patients had left the study."

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		9902-292	**Immunization of Patients with Metastatic Melanoma Using a Recombinant Fowlpox Virus Encoding a GP 100 Peptide Preceded by an Endoplasmic Reticulum Insertion Signal Sequence. Sponsor: NCI-Cancer Therapy Evaluation Program (NCI-CTEP)**	
187	07/19/2001		*Other:*	Notification from the PI that an individual enrolled in this trial did not have the correct HLA subtype. This individual has not experienced any events that have been unexpected.
		9903-296	**Phase I Trial of Immunotherapy with Adenovirus-Interferon-Gamma (TG1041) in Patients with Malignant Melanoma. Sponsor: Transgene, Inc.**	
163	06/29/2001		*Status Change:*	Trial has been closed to further enrollment by the sponsor. The sponsor plans to employ a newer generation adenoviral vector (containing E4) expressing interferon-gamma from a CMV promoter.
		9903-297	**Intensive Immunosuppression Followed by Rescue with CD34 Selected, T Cell Depleted, Leukopheresis Products in Patients with Multiple Sclerosis.**	
214	05/14/2001		*Protocol Change:*	This amendment allows for the addition of several laboratory and radiologic studies and the deletion of several others. These changes do not change the major analysis of the protocol nor should they impact the safety analysis of this study. As of this date, there have been no SAEs submitted to OBA for this protocol.
		9903-303	**Tumor Purging of Autologous Stem Cell Grafts in Children with High-Risk Solid Tumors: Transplantation of Retrovirally Marked Stem Cell Grafts Purified by CD34+ Antibody Selection and High-Speed Cell Sorting.**	
221	08/01/2001		*PI or Site Change:*	Dr. John M. Cunningham has replaced Dr. Bowman as the PI at St. Jude Children's Research
		9904-304	**Pediatric Phase I Study of AdV/RSV-TK Followed by Ganciclovir for Retinoblastoma**	
153	06/14/2001		*Other:*	Received copies of the IBC and IRB approvals for the amendment submitted to OBA on 3-20-01.

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		9904-307	**Phase I Trial of Immunotherapy with MVA-HPV-IL2 (TG4001) in Women with Cervical Intraepithelial Neoplasia (CIN) Grade 3. Sponsor: Transgene, Inc.**	
165	06/19/2001		*Protocol Change:*	Definition of maximum tolerated dose has been modified to state that toxicities will now be graded in accordance with World Health Organization criteria. "Dose limiting toxicity is defined as the level at which no grade 3 or 4 toxicities (except alopecia), thought to be related to the treatment, are observed." The immunology evaluation section has been expanded. The exclusion criteria have been amended to include individuals, or immediate household contacts, "...with a history of eczema, exfoliative skin disorders, pregnancy, or other immunocompromise offering an increased risk for disseminated vaccinia infection." Finally, cervical biopsy has been added to the baseline visit. The purpose of this additional biopsy is to obtain sufficient tissue for immunohistochemistry analysis.
		9906-321	**A Phase I Study of E1B-Attenuated Replication Competent Adenovirus Vector-Mediated Intratumoral Administration of the E. coli Cytosine Deaminase/HSV-1 Thymidine Kinase Fusion Gene in Conjunction with Two Prodrugs, 5-Fluorocytosine and Ganciclovir for Patients with Local Recurrence of Prostate**	
181	07/30/2001		*Annual Update:*	Received copy of annual report that was submitted to the FDA.
		9906-322	**A Phase I Study of NGF Ex Vivo Gene Therapy for Alzheimer's Disease**	
194	05/17/2001		*Annual Update:*	To date, two individuals have been enrolled on this study. One has received the study agent and the other is due to receive study agent in July.
162	06/29/2001		*Annual Update:*	A copy of the cover letter sent to the FDA documenting the types of tests being performed on he vector product was submitted.

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		9907-327	**A Phase I Double-Blind, Placebo Controlled, Escalating Dose, Multi-Center Study of Ad2/Hypoxia Inducible Factor (HIF)-1-alpha/VP16 Gene Transfer Administered by Intramuscular Injection to Patients with Critical Limb Ischemia Who are Not Candidates for Surgical or Percutaneous Revascularization. Sponsor:**	
223	05/17/2001		*Protocol Change:*	The sposnsor, Genzyme, has been in contact with the FDA regarding the streamlining of reporting of adverse events in this trial. Genzyme wanted to clarify the reporting requirements for reporting events for individuals who have not fully enrolled (as defined by Genzyme) into this trial. The sponsor has defined individual participant enrollment as occurring once an individual has been randomized. Randomization in this trial is composed of two parts. The first occurs when an individual has completed all of the prerequisite screening procedures and is determined to meet the eligibility criteria. The second part of the randomization process occurs on day 1 of the trial, when the study participant receives injections of the study agent. Adverse events that occur to a participant prior to randomization will not be reported on an expedited manor unless associated with a "...specific study screening procedure, outside of the standard of care." These events will still be reported to the sponsor on Genzyme's reporting form as well as on the adverse event case report form, and considered to be a "pre-treatment
		9910-346	**A Phase II, Randomized, Multicenter, 26-Week Study to Assess the Efficacy and Safety of CI-1023 Delivered Through Minimally Invasive Surgery Versus Maximum Medical Treatment in Patients with Severe Angina, Advanced Coronary Artery Disease, and No Options for Revascularization. Sponsor: Parke-Davis**	
203	07/03/2001		*PI or Site Change:*	Dr. Michael Frank at Evanston Northwestern Healthcare, Evanston IL is now a PI.
182	07/27/2001		*PI or Site Change:*	Dr. A. R. J. Rajakumar at Royal University Hospital, University of Saskatchewan, Saskatoon, Canada is now an investigator on this trial.

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		9910-350	**A Phase I Dose Escalation Study of Intraperitoneal E1A-Lipid Complex (1:3) with Combination Chemotherapy in Women with Epithelial Ovarian Cancer. Sponsor: Targeted Genetics Corporation**
216	05/18/2001	*Annual Update:*	This amendment clarifies the definition of what constitutes a dose limiting toxicity in safety laboratory study results, and states that one of the centers has promoted the sub-investigator to principal investigator status. These changes do not change the protocol significantly and will help clarify the definition of SAEs. This amendment was used as an opportunity to look over the SAE profile for this protocol. There have been several reports to the file, with one that has been addressed in much detail by the sponsor (Targeted Genetics). This involved a case in which the study subject developed nausea, emesis, abdominal pain, hypotension and fever in short time proximity to receiving intraperitoneal product. This subject was the first one enrolled in the study and received 3mg of DNA. Due to the nature and timing of this incident, it was considered to be an allergic reaction to the gene transfer product (E1a gene-lipid complex). In order to see if such a reaction had occurred before, two prior protocols utilizing a E1a-lipid complex were looked at. These were protocols 162 (for head and neck cancer patients) and 137 (for metastatic breast and ovarian cancer patients). Both of these studies were conducted by the same corporate sponsor, and though using a lipid complex, it differs from that used in protocol 350. In study 162, there was one possibly related SAE (of 12 subjects) where an elderly male developed acute mental status changes. These were classified as moderate in severity and thought to be related either to the injection of gene transfer product or due to the hypercalcemia that occurred secondary to the cancer. It resolved with therapy of the hypercalcemia. In study 137, 18 subjects were enrolled (6 with breast cancer and receiving multiple injections into the pleural cavity when metastases to this area were found; 12 with ovarian cancer receiving multiple injections ip [intraperitoneal] when peritoneal metastases were found). The breast cancer arm was dropped after the 6th subject due to AEs (essentially fever and pain). In the ovarian cancer arm, the 7.2 mg dose (high-dose) was tried in 3 subjects and due to SAEs this dosing level was dropped. All prior and subsequent patients received a 3.6 mg dose per injection. In general, it seems that the majority of the i.p. subjects experienced abdominal pain, nausea, emesis and fever within 24-48 hours of receiving gene transfer product. Several subjects developed obstipation, with one severe enough that an ileostomy was required to relieve the abdominal obstruction. One subject developed ascites and one had their i.p. catheter develop an acute bacterial infection. Similarly to the case in study 350, two subjects had acute onset (within 20-40 minutes) allergic reactions, with nausea, emesis, abdominal pain, fever, and hypotension. Unlike the case in study 350, these two subjects did not require

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				substantial intravenous fluid boluses to resolve the hypotension, but responded to the use of diphenhydramine and steroids. Several things should be noted: a. As per the corporate sponsor (on their website), studies 137 and 162 demonstrated a favorable safety record, with no mention of the SAEs noted above. b. The use of any product intraperitoneally can lead to inflammation. Thus, the development of these SAEs is not surprising and such events were not seen in the head and neck study (Study 162, which involved intratumoral injection). c. Patients with ovarian cancer and peritoneal metastases do develop abdominal obstruction and adhesions commonly. Nausea and emesis are also common events seen as sequelae of this cancer spread.
200	07/09/2001		*PI or Site Change:*	Dr. Howard Muntz is now the PI at Virginia Mason Medical Center, Seattle, WA.
		9912-360	**Treatment of Patients with Metastatic Melanoma Using Cloned Lymphocytes Following the Administration of a Nonmyeloablative But Lymphocyte Depleting Regimen.**	
180	07/24/2001		*Protocol Change:*	Received a copy of the revised clinical protocol that incorporates the amendment to allow for intra-arterial administration of cells.
179	07/24/2001		*Annual Update:*	Annual update dated June 18, 2001 In the past year, an additional 5 individuals have entered into this study. Two individuals have been enrolled under a compassionate exemption that also allowed for intra-arterial administration. An amendment, according the PI, is pending approval that would allow for s pending approval that would allow for arterial administration.

ID #	Letter	Protocol #	Amendment Description	
		9912-366	**A Phase III Multi-Center, Open-Label, Randomized Study to Compare the Overall Survival and Safety off Bi-Weekly Intratumoral Administration of RPR/INGN 201 Versus Weekly Methotrexate in 240 Patients with Refractory Squamous Cell Carcinoma of the Head and Neck (SCCHN). Sponsor: Aventis Pharmaceuticals - Gencell Division (formerly Rhone-Poulenc Rorer)**	
168	05/30/2001		*PI or Site Change:*	Dr. Randall Breau at the University of Arkansas for Medical Sciences, Little Rock, AR is now an investigator on this trial.
167	06/15/2001		*PI or Site Change:*	Dr. Fred Rosen at The University of Illinois at Chicago is now an investigator on this trial.
204	07/06/2001		*PI or Site Change:*	Dr. Jeffrey Giguere at the Cancer Center of the Carolinas is now a PI.
184	07/26/2001		*Other:*	Administrative changes have been made for contact information and to change study agent name from RPR/INGN 201 to INGN 201.
		0001-371	**A Phase I Safety Study in Patients with Severe Hemophilia B (Factor IX Deficiency) Using Adeno-Associated Viral Vector to Deliver the Gene for Human Factor IX into the Liver.**	
217	07/20/2001		*PI or Site Change:*	Dr. Catherine Manno at the Children's Hospital of Philadelphia is now a PI.
		0001-372	**A Phase 1, Single-Dose, Dose-Escalation Study of MiniAdFVIII Vector in Patients with Severe Hemophilia A. Sponsor: GenStar Therapeutics Corporation**	
150	06/06/2001		*PI or Site Change:*	Dr. Ralph A. Gruppo at the Children's Hospital Medical Center, Cincinnati, Ohio is now an investigator on this trial.
		0001-382	**A Pilot Study of Gene Modified Autologous Neuroblastoma Vaccine for the Post-Chemotherapy Treatment of High Risk Neuroblastoma.**	
197	07/17/2001		*PI or Site Change:*	Dr. Heidi Russell is now the PI at the Baylor College of Medicine.

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		0001-385	**Phase I/II Study of GM-CSF Gene-Modified Autologous Tumor Vaccines in Early and Advanced Stage Non-Small Cell Lung Cancer (NSCLC). Sponsor: Cell Genesys, Inc.**	
224	07/11/2001		*Annual Update:*	Received a copy of the annual report as submitted to the FDA.
		0001-387	**A Randomized, Double-Blind, Placebo-Controlled, Multicenter, 12-Week Follow-up, Pilot Study of the Tolerability and Feasibility of Administering ADGVVEGF121.10 (CI-1023) Via the Biosense Intramyocardial Injection Device to Patients with Advanced Coronary Artery Disease. Sponsor: Parke-Davis Pharmaceutical**	
183	08/06/2001		*PI or Site Change:*	Dr. Jeffrey Moses at Lenox Hill Hospital, New York is now an investigator on this trial.
		0002-388	**A Double-Blind, Randomized, Placebo-Controlled, Dose-Ranging, 26-Week Study to Assess the Safety and Efficacy of CI-1023 (ADGVVEGF121.10) in Peripheral Arterial Disease Patients with Severe, Disabling Intermittent Claudication. Sponsor: Parke-Davis Pharmaceutical Research**	
205			*PI or Site Change:*	Dr. James Hermiller at the Care Group, Indianapolis, IN is now a PI.
160	05/22/2001		*PI or Site Change:*	Dr. Alan Tenaglia at Tulane University Health Sciences Center, New Orleans, LA is now an investigator on this trial.
198	05/24/2001		*PI or Site Change:*	Dr. Jorge Saucedo at the University of Arkansas for Medical Sciences, Little Rock is now an investigator on this trial.
169	05/29/2001		*PI or Site Change:*	Dr. Michael Azrin at the University of Connecticut Health Center, Farmington, CT is now an investigator on this trial.

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172	05/30/2001		*PI or Site Change:*	Dr. Paul Gagne at the New York University School of Medicine is now a PI.
213	06/18/2001		*PI or Site Change:*	Dr. Farrell Mendelsohn at the Baptist Health System, Birmingham, AL is now a PI.
			Other:	As per the informed consent document, the injections (with either placebo or with the gene transfer product) will be done in an outpatient cardiology clinic office. Sterile procedures will be used in regard to injection site preparation and during the procedure, but the question still arises about proper handling of the vials prior to injection. As per the study protocol (which will be followed by Dr. Mendelsohn without revisions) the vials are to be prepared at a pharmacy using Biosafety level 2 precautions. All vials will be prepared aseptically in a biosafety cabinet. Air will be evacuated from the vials prior to being shipped to the investigators. Thus, aerosolization of product will be of minimal concern. Full details of these procedures are described in Appendix A.2 of the study protocol.
196	07/13/2001		*PI or Site Change:*	Dr. Navil Dib at the Arizona Heart Institute & Foundation, Phoenix, AZ is now a PI.
		0002-391	**Phase II Study of Leuvectin in Patients with Metastatic Renal Cell Carcinoma. Sponsor: Vical Inc.**	
151	06/29/2001		*Status Change:*	Notification from sponsor that interim analysis of data from the first 37 individuals indicated that the level of IL-2 expression was dramatically lower than in other trials with the same vector. This study employed a vector that was formulated with a different process. Due to a lack of sufficient efficacy in these first 37 individuals, this trial is no longer being continued.

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		0005-395	**A Phase I/II Trial Investigating the Safety and Immunotherapy of Adenovirus Encoding the Melan-A/MART-1 and gp100 Melanoma Antigens Administered Intradermally to Patients with Stage II-IV Melanoma. Sponsor: Genzyme Corporation**	
195	06/27/2001		*Protocol Change:*	Due to a concern over the amount of blood to be drawn, certain tests will only be performed at the screening stage and will not be repeated at the time baseline measurements are taken.
		0005-399	**An Open-Label, Phase I, Dose-Escalation Study of Tumor Necrosis Factor-alpha (TNFeradeTM Biologic) Gene Therapy with Radiation Therapy for Locally Advanced, Recurrent, or Metastatic Solid Tumors.**	
190	07/19/2001		*Protocol Change:*	Changes have been made to clarify eligible individuals and follow-up studies to be performed: viral shedding, physical examine, hematology and chemistry. In addition, biopsies are now optional for all administration sites and for all individuals participating in this trial.
		0005-400	**Transfer of the Multidrug Resistance Gene, MDR-1, to Hematopoietic Progenitors from Patients with High Risk Lymphoma.**	
164	05/18/2001		*PI or Site Change:*	Dr. Stewart at U. Massachusetts Memorial Health Care is no longer a PI for this trial.
			Annual Update:	A revised clinical protocol and informed consent document were provided to indicate that Dr. Becker is the sole PI for this study. Individuals have not been accrued as of this date. Investigator anticipates accrual to start this summer. Other changes have been made that reflect different suppliers of products, not the vector, employed in the trial. In addition, the protocol has been amended to state that "vincristine will be dose reduced or discontinued as described..." The trial now clearly states that there will not be any dose escalation of vincristine. Finally, "end of therapy" has been defined as "one month post transplant" and "post treatment" is defined as "3, 6, and 12 months post transplant."

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		0006-404	**A Multicenter, Double-Blind, Placebo-Controlled, Phase II Study of Aerosolized AAVCF in Cystic Fibrosis Patients with Mild Lung Disease. Sponsor: Targeted Genetics**	
220	06/27/2001		*PI or Site Change:*	Dr. L. Terry Spencer at the University of Florida, Gainesville, FL is now a PI.
215	07/13/2001		*Annual Update:*	The purpose of this update is to notify OBA that the Cystic Fibrosis Foundation, after review by its Data Monitoring Committee, has recommended that this study proceed and that the age limit be lowered from 18 years of age to 15 years. The Data Monitoring Committee reviewed data from the first 5 patients enrolled in this study (primary investigator being Dr. Moss at Stanford) and found no serious adverse events or grade 3 or 4 adverse events. The study has recently enrolled several other study centers so as to increase the number of subjects that can be enrolled quickly.
		0007-407	**A Phase I Double-blind, Placebo-Controlled, Escalating Dose, Multi-center Study of Ad2/Hypoxia Inducible Factor (HIF)-1-alpha/VP16 Gene Transfer Administration by Intramyocardial Injection During Coronary Artery Bypass Grafting (CABG) Surgery in Patients with Areas of Viable and Underperfused Myocardium not Amenable to Bypass Grafting or Percutaneous Intervention. Sponsor: Genzyme Corporation**	
222	05/17/2001		*Protocol Change:*	The sponsor, Genzyme, has been in contact with the FDA regarding the streamlining of reporting of adverse events in this trial. Genzyme wanted to clarify the reporting requirements for reporting events for individuals who have not fully enrolled (as defined by Genzyme) into this trial. The sponsor has defined individual participant enrollment as occurring once an individual has been randomized. Randomization in this trial is composed of two parts. The first occurs when an individual has completed all of the prerequisite screening procedures and is determined to meet the eligibility criteria. The second part of the randomization process occurs during surgery, when it is determined that an individual is not a candidate for conventional revascularization options and therefore receives administration of study agent. Adverse events that occur to a participant prior to randomization will not be reported on an expedited manor unless associated with a "...specific study screening procedure, outside of the standard of care." These events will still be reported to the sponsor on Genzyme's reporting form as well as on the adverse event case report form, and considered to be a "pre-treatment."

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159	05/24/2001		*Protocol Change:*	Notification from sponsor that an individual enrolled in this trial received study agent without receiving coronary artery bypass. According to the currently approved clinical protocol, study agent is not to be administered unless coronary artery bypass is also performed. In this one individual, the investigator, during open-heart surgery, determined that the individual was not an acceptable candidate for bypass grafting. The sponsor (Genzyme) has reminded all investigators that the protocol does not permit administration of the study agent to individuals deemed ineligible, even if the determination is made during surgery, for bypass grafting. Genzyme is seeking clearance from the FDA and the IRBs involved to allow for study agent administration in the absence of bypass grafting, when it is determined that the graft cannot be performed due to unanticipated surgical complications.
175	08/06/2001		*PI or Site Change:*	Dr. Omar Lattouf at Emory University School of Medicine, Atlanta, GA is now an investigator on this trial.
		0009-412	**A Phase III, Multi-Center, Open-Label, Randomized Study to Compare the Effectiveness and Safety of Intratumoral Administration of RPR/INGN 201 in Combination with Chemotherapy Versus Chemotherapy Alone in 288 Patients with Recurrent Squamous Cell Carcinoma of the Head and Neck (SCCHN). Sponsor: Aventis Pharmaceuticals - Gencell Division**	
174	05/16/2001		*PI or Site Change:*	Dr. W. Jarrard Goodwin at the University of Miami Hospital and Clinics, Miami, FL is now an investigator on this trial.
156	05/22/2001		*PI or Site Change:*	Dr. Bruce Brockstein at Evanston Hospital, Evanston IL; Dr. William Flood at The Milton S. Hershey Medical Center, Hershey, PA; and Dr. Greg Krempl at University Hospital, Oklahoma City, OK are now investigators on this trial.
185	07/26/2001		*Other:*	Administrative changes have been made for contact information and to change study agent name from RPR/INGN 201 to INGN 201.

ID #	Letter	Protocol #	Amendment Description	
		0010-417	**Tumor Site Specific Phase I/II Evaluation of Safety and Efficacy of Hepatic Arterial Infusion of a Matrix-Targeted Retroviral Vector Bearing a Dominant Negative Cyclin G1 (dnG1) Construct as Treatment for Colorectal Carcinoma Metastatic to Liver.**	
189	07/17/2001		*Other:*	Notification from sponsor of the trial, Dr. Gordon, of irregularities in testing the master cell bank. Outside, independent, consultants were employed to prepare and test the master cell bank. In turn, the consultants indicated to the sponsor that they employed an independent laboratory to conduct sterility testing. However when the sponsor contacted the independent laboratory directly, they were informed that the sterility testing was not performed by this laboratory. The sponsor has suspended use of this master bank and has made arrangements for the production of a new bank.
		0010-420	**Phase I, Prospective, Placebo Controlled, Randomized Assessment of Direct Administration of a Replication Deficient Adenovirus Vector (Ad_{CU}VEGF121.1) Containing the VEGF121 cDNA to the Ischemic Myocardium of Individuals with Diffuse Coronary Artery Disease as an Adjunct to Coronary Bypass**	
193	06/28/2001		*PI or Site Change:*	Dr. Todd Rosengart at Evanston Northwestern Healthcare, Evanston, IL is now an investigator on this trial.
		0010-424	**Developmentally Regulated Endothelial Locus (Del- 1) Gene Medicine (VLTS-589) A Phase I Multi-Center, Open-Label, Single-Dose Escalation Clinical Safety Trial of VLTS-589 for the Treatment of Patients with Peripheral Arterial Disease. Sponsor: Valentis, Inc.**	
230	06/11/2001		*PI or Site Change:*	Dr. Marc Litt at the Jacksonville Heart Center, Jacksonville, FL and Dr. Ronald Karlsberg at the Cardiovascular Research Institute, Beverly Hills, CA are now PIs.
218	07/24/2001		*PI or Site Change:*	Dr. Jeffrey W. Olin at the Heart and Vascular Institute of New Jersey, Morristown, NJ is now a PI.

ID #	Letter	Protocol #		Amendment Description
		0011-431	**A Phase II Study of High-Dose Allovectin-7 in Patients with Advanced Metastatic Melanoma. Sponsor: Vical**	
161	06/28/2001		*Protocol Change:*	Changes in the trial include: Removal of the provision for alteration of dose levels following a grade 2 toxicity. And provisions were added for early recognition of specific drug-related grade 2 toxicities.
219	06/29/2001		*PI or Site Change:*	Dr. Jose Lutzky at Mt. Sinai Comprehensive Cancer, Miami, FL is now a PI.
154	07/03/2001		*PI or Site Change:*	Dr. Agop Y. Bedikian at the University of Texas, MD Anderson Cancer Center, Houston, TX is now an investigator on this trial.
		0011-432	**A Phase II Study of Safety and Efficacy of Allovectin-7 Immunotherapy for the Treatment of Primary Resectable Squamous Cell Carcinoma of the Oral Cavity or Oropharynx. Sponsor: Vical Inc.**	
202	07/13/2001		*PI or Site Change:*	Dr. Gregory Weinstein at The Hospital of the University of Pennsylvania is now a PI.
		0101-457	**An Open-Label, Phase I, Dose-Escalation Study of TNFeradeTM Biologic with Radiation Therapy as an Adjunct to Surgery or for Palliation of Soft Tissue Sarcoma of the Extremities. Sponsor: GenVec.**	
191	07/19/2001		*Protocol Change:*	Changes have been made to clarify the timing of sampling post-study agent administration. Studies to be performed at the 6 and 12 month follow-up have been amended.